

Horizon Scanning in Oncology

Regorafenib (Stivarga®) for
heavily pretreated patients
with metastatic colorectal
cancer



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1 Drug description

Generic/Brand name/ATC code:

Regorafenib/Stivarga®/L01XE21

Developer/Company:

Bayer Pharma AG

Description:

Regorafenib (Stivarga®) is a multi-kinase inhibitor that targets angiogenic, stromal and oncogenic receptor tyrosine kinases [1]. It binds to vascular endothelial growth factor receptors (VEGFRs) 2 and 3, which are important for tumor angiogenesis, and to receptor tyrosine kinases RET, KIT, PDGFR and RAF, which are involved in tumor cell signaling. Regorafenib thus inhibits tumor angiogenesis and tumor cell proliferation [2].

Regorafenib is administered at a dosage of 160 mg (four 40 mg tablets), once daily for the first 21 days of each 28-day cycle. The drug has to be taken orally, due to effects on pharmacokinetics, with a low-fat breakfast. The treatment should be continued until disease progression or unacceptable toxicity occurs [3].

**regorafenib inhibits
tumor angiogenesis and
tumor cell proliferation**

oral administration

2 Indication

Regorafenib (Stivarga®) is indicated in patients with metastatic colorectal cancer (mCRC) who have been previously treated with:

- ✿ a fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy
- ✿ an anti-VEGF therapy
- ✿ an anti-EGFR therapy (if KRAS wild-type) [3].

**for heavily pretreated
patients with mCRC**

3 Current regulatory status

In August 2013, the EMA granted marketing authorization for Stivarga® for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy) [4].

The FDA approved regorafenib (Stivarga®) on September 27, 2012 [5] for patients with mCRC who have been pretreated with:

- ✿ A fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy
- ✿ an anti-VEGF therapy
- ✿ an anti-EGFR therapy (if KRAS wild-type).

**approved by the EMA
and the FDA**

In February 2013, the FDA approved regorafenib (Stivarga®) for the treatment of patients with advanced gastrointestinal stromal tumors (GIST) that cannot be surgically removed and no longer respond to other FDA-approved treatments for this disease [6].

In Switzerland, Stivarga® has been approved for the treatment of patients with mCRC who were previously treated with a fluoropyrimidine-, oxaliplatin- and irinotecan-based therapy, anti-VEGF therapy and anti-EGFR (in case of KRAS wild-type) on February 27, 2013 [7]. In Japan, marketing authorization for Stivarga® for the treatment of unresectable advanced or recurrent colorectal cancer was granted on March 25, 2013 [8].

4 Burden of disease

Colorectal cancer (CRC) develops in the tissues of the colon and/or rectum. It is the third most common cancer in men and women in the western countries.

**incidence rate in Austria
28.1 per 100,000 people
per year**

Due to early detection and treatment, incidence rates are declining [9]. In Austria, CRC is the third most common malignancy diagnosed in men and the second most common malignancy diagnosed in women. In 2010, the incidence rate in Austria for both men and women was 28.1 (per 100,000 people per year), mortality rate was 11.9 (per 100,000 people per year) [10].

**median age at diagnosis:
69 years**

Median age at diagnosis for CRC is about 69 years [11]; the 1-year relative survival rate for persons with CRC is 84% and the 5-year relative survival rate is 64% (relative survival compares survival among cancer patients to that of people not diagnosed with cancer who are of the same age, race and sex) [9].

Histologically, more than 95% of CRCs are adenocarcinomas. Less common types are carcinoid tumors, gastrointestinal stromal tumors, lymphomas or sarcomas [12].

Risk factors for CRC are increasing age, a personal or family history of CRC and/or polyps, a personal history of chronic inflammatory bowel disease as well as hereditary conditions (for example Lynch syndrome and familial adenomatous polyposis). Moreover, type 2 diabetes, obesity, physical inactivity, a diet high in red or processed meat, alcohol consumption, long-term smoking and possibly very low intake of fruit and vegetables are associated with an increased risk for CRC. There are factors that appear to decrease the risk, such as the consumption of milk and calcium or higher blood levels of vitamin D [9].

**approximately 20% of
patients have
metastases at the time
of diagnosis**

Common symptoms of CRC are bloody or tarry stool, abdominal pain, otherwise unexplained iron deficiency anemia and/or changes in bowel habits. Less common symptoms are abdominal distension, and/or nausea and vomiting. Straining to defecate, rectal pain or small-caliber stools indicate that the tumor is located in the rectum. CRC is a potentially metastatic disease; the most frequently affected sites are the regional lymph nodes, the liver, the lungs and the peritoneum. Approximately 20% of patients have metastases at the time of diagnosis. The preferred staging system for CRC is the TNM classification: primary tumor (T), regional lymph node (N), distant metastasis (M) [13].

5 Current treatment

A large number of treatment options are available for CRC. Selection of therapy depends on the site and extent of metastatic disease, performance status, organ function and comorbidity of the patient [14].

If patients qualify for intensive therapy, options for the treatment of advanced or metastatic disease are the following [15]:

options for first-line therapy

- ✿ FOLFOX (fluorouracil, leucovorin, oxaliplatin) ± bevacizumab
- ✿ CapeOX (capecitabine, oxaliplatin) ± bevacizumab
- ✿ FOLFOX ± panitumumab (KRAS wild-type gene only)
- ✿ FOLFIRI (fluorouracil, leucovorin, irinotecan) + bevacizumab
- ✿ FOLFIRI ± cetuximab or panitumumab (KRAS wild-type gene only)
- ✿ 5-FU/leucovorin or capecitabine ± bevacizumab
- ✿ FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)

In case of disease progression after these first-line therapies, treatment options will be selected according to the first-line regimen and include:

options after first progression

- ✿ FOLFIRI ± bevacizumab
- ✿ FOLFIRI ± ziv-aflibercept
- ✿ Irinotecan ± bevacizumab
- ✿ Irinotecan ± ziv-aflibercept
- ✿ FOLFIRI ± cetuximab or panitumumab (KRAS wild-type gene only)
- ✿ Cetuximab or panitumumab (KRAS wild-type gene only) + irinotecan
- ✿ FOLFOX ± bevacizumab
- ✿ CapeOX ± bevacizumab

Therapy after second progression will again depend on previously used regimens and include:

for further lines of therapy

- ✿ Cetuximab or panitumumab + irinotecan
- ✿ FOLFOX or CapeOX
- ✿ Regorafenib
- ✿ Clinical trial
- ✿ Best supportive care (BSC)

For later lines of therapy, the remaining treatment options are limited:

very few options for heavily pre-treated patients

- ✿ Clinical trial
- ✿ BSC [15].

6 Evidence

A literature search was conducted on the 13th of June 2013 in four databases (Medline, Embase, CRD, and The Cochrane Library). Search terms were “Colorectal Neoplasms/Cancer”, “(Neoplasm) Metastasis”, “Regorafenib”, “Stivarga” and “bay 73”.

one phase III study and
one meta-analysis
included

Also, the manufacturer was contacted for any further evidence, and submitted 24 studies. Of these, 16 had already been identified by the systematic literature search, resulting in 8 additional references.














Overall, 87 references were identified of which two have been included in this report:

- ✚ a phase III study, assessing the effect of regorafenib on patients with mCRC that keeps progressing after administration of all approved standard therapies (CORRECT trial) [16] and
- ✚ a meta-analysis, evaluating the risk of hand-foot skin reactions in patients treated with regorafenib [17].

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial [16].			
Study identifier	NCT01103323, EudraCTNumber: 2009-012787-14, CORRECT trial		
Design	International, multicenter, randomized (2:1 ratio), placebo-controlled		
	Duration	<i>Enrolment:</i> 2010-04-30 to 2011-03-22 <i>Median follow-up:</i> NA <i>Cut-off dates for second interim analyses:</i> 2011-07-21	
Hypothesis	Superiority (90% power to detect a 33.3% increase in median OS, assuming a 4.5 month median OS for the placebo group (i.e. HR of 0.75 for regorafenib over placebo))		
Funding	Bayer HealthCare Pharmaceuticals		
Treatment groups	Intervention (N=505)	Regorafenib 160 mg (oral) once daily for the first 3 weeks of each 4-week cycle + BSC (excluding other investigational antitumor agents or neoplastic chemotherapy, hormonal therapy, and immunotherapy)	
	Control (N=255)	Placebo once daily for the first 3 weeks of each 4-week cycle + BSC (excluding other investigational antitumor agents or neoplastic chemotherapy, hormonal therapy, and immunotherapy)	
Endpoints and definitions	Overall survival (primary outcome)	OS	Time from randomization to death from any cause
	Progression-free survival	PFS	Time from randomization to first radiological or clinical observation of disease progression or death from any cause
	Objective tumor response rate	ORR	Proportion of patients with complete or partial response

Endpoints and definitions	Disease control rate	DCR	Proportion of patients with a best response of complete or partial response or stable disease; assessment of stable disease had to be made at least 6 weeks after randomization		
	Safety	-	-		
	Duration of response and stable disease	DOR	NA		
	Health-related quality-of-life and health utility values	Hr-QoL	Measured with:  EORTC general health status and QLQ-C30  EQ-5D  EQ-5D VAS		
Results and analysis					
Analysis description	Intention-to-treat analysis OS and PFS: compared between treatment groups with stratified log-rank test HRs (with 95% CI) were calculated with Cox model (adjusting for stratification factors); Kaplan-Meier survival estimates were calculated for each treatment group Objective response and disease control rates were compared between treatment groups with Cochran-Mantel-Haenszel test (adjusting for stratification factors)				
Analysis population	Inclusion	 Histological or cytological documentation of adenocarcinoma of the colon or rectum			
		 Prior locally and currently approved standard therapies including fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild-type)			
		 Disease progression during or within 3 months following the last administration of approved standard therapy or discontinuation of standard therapy because of unacceptable toxic effects			
		 Measurable or non-measurable disease according to Response Evaluation Criteria in Solid Tumors criteria, Version 1.1			
		 ECOG performance status of ≤1			
		 Life expectancy of at least 3 months			
	Exclusion	 Prior treatment with regorafenib			
 Previous assignment to treatment during this study					
Characteristics	Exclusion	 Previous or concurrent cancer that is distinct in primary site or histology from CRC within 5 years before randomization except for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors			
		 Major surgical procedures, open biopsy or significant traumatic injury within 28 days before start of study medication			
		Characteristics		Intervention	Control
		Median age/IQR, years		61/54-67	61/54-68
		Sex, % male/female		62/38	60/40
		ECOG performance Status, % 0/1		52/48	57/43
Primary site of disease Colon/rectum/colon and rectum, %		64/30/6	68/27/5		

Analysis population	Characteristics	KRAS mutation, % no/yes/unknown	41/54/5	37/62/2
		BRAF mutation, % no/yes	96/4	98/2
		Adenocarcinoma, %	98	96
		Number of previous systemic anticancer therapies, % 1-2/3/≥4	27/25/49	25/28/47
		Previous Bevacizumab, %	100	100
		Time from diagnosis of metastasis (median, months)/IQR	31/21-43	30/20-46
Descriptive statistics and estimated variability	Treatment group		Intervention (Regorafenib + BSC)	Control (Placebo + BSC)
	Number of subjects		N = 505	N = 255
	OS median, months IQR		6.4 3.6-11.8	5.0 2.8-10.4
	OS rate, % at 3/6/9/12 months		80.3/52.5/38.2/24.3	72.7/43.5/30.8/24.0
	PFS median, months IQR		1.9 1.6-3.9	1.7 1.4-1.9
	Objective response rate, %		1.0	0.4
	Duration of stable disease median, months IQR		2.0 1.7 - 4.0	1.7 1.4 - 1.9
	Disease control rate, %		41	15
	EORTC QLQ-C30, score at baseline at end of treatment		62.6 48.9	64.7 51.9
	EQ-5D, score at baseline at end of treatment		0.73 0.59	0.74 0.59
	EQ-5D, VAS score at baseline at end of treatment		65.4 55.5	65.8 57.3

Effect estimate per comparison	Comparison groups	Intervention vs Control	
		HR	95% CI
	OS	HR	0.77
		95% CI	0.64-0.94
		P value	0.0052
	OS in subgroup colon cancer	HR	0.70
		95% CI	0.56-0.89
		P value	NR
	OS in subgroup rectal cancer	HR	0.95
		95% CI	0.63-1.43
		P value	NR
	PFS	HR	0.49
		95% CI	0.42-0.58
		P value	<0.0001
	PFS in subgroup colon cancer	HR	0.55
		95% CI	0.45-0.67
		P value	NR
	PFS in subgroup rectal cancer	HR	0.45
		95% CI	0.33-0.62
		P value	NR
	ORR	HR	NR
		95% CI	NR
		P value	0.19
	DCR	HR	NR
		95% CI	NR
		P value	P<0.0001

Abbreviations: BRAF = B-type Raf kinase, BSC = best supportive care, CI = confidence interval, CRC = colorectal cancer, ECOG = Eastern Cooperative Oncology Group, EORTC = European Organisation for Research and Treatment of Cancer, EQ-5D = EuroQol five dimension, HR = hazard ratio, IQR = interquartile range, KRAS = Kirsten rat sarcoma, NA = not available, NCT = National Clinical Trial, NR = not reported, OS = overall survival, ORR = overall response rate, PFS = progression-free survival, QLQ-C30 = quality-of-life questionnaire, VAS= visual analogue scale

Table 2: Most frequent adverse events (occurring in $\geq 5\%$ of patients in either group from start of treatment to 30 days after end of treatment, safety population)

NCT01103323						
Adverse Event (according to NCI-CTCAE version 3.0)	Regorafenib + BSC (N=500)			Placebo + BSC (N=253)		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any event	465 (93)	253 (51)	17 (3)	154 (61)	31 (12)	4 (2)
Fatigue	237 (47)	46 (9)	2 (<1)	71 (28)	12 (5)	1 (<1)
Hand-foot skin reaction	233 (47)	83 (17)	0	19 (8)	1 (<1)	0
Diarrhea	169 (34)	35 (7)	1 (<1)	21 (8)	2 (1)	0
Anorexia	152 (30)	16 (3)	0	39 (15)	7 (3)	0
Voice changes	147 (29)	1 (<1)	0	14 (6)	0	0
Hypertension	139 (28)	36 (7)	0	15 (6)	2 (1)	0
Oral mucositis	136 (27)	15 (3)	0	9 (4)	0	0
Rash or desquamation	130 (26)	29 (6)	0	10 (4)	0	0
Nausea	72 (14)	2 (<1)	0	28 (11)	0	0
Weight loss	69 (14)	0	0	6 (2)	0	0
Fever	52 (10)	4 (1)	0	7 (3)	0	0
Constipation	42 (8)	0	0	12 (5)	0	0
Dry skin	39 (8)	0	0	7 (3)	0	0
Alopecia	36 (7)	0	0	1 (<1)	0	0
Taste alteration	35 (7)	0	0	5 (2)	0	0
Vomiting	38 (8)	3 (1)	0	13 (5)	0	0
Sensory neuropathy	34 (7)	2 (<1)	0	9 (4)	0	0
Nose bleed	36 (7)	0	0	5 (2)	0	0
Dyspnea	28 (6)	1 (<1)	0	4 (2)	0	0
Muscle pain	28 (6)	2 (<1)	0	7 (3)	1 (<1)	0
Headache	26 (5)	3 (1)	0	8 (3)	0	0
Pain, abdomen	25 (5)	1 (<1)	0	10 (4)	0	0
Thrombocytopenia	63 (13)	13 (3)	1 (<1)	5 (2)	1 (<1)	0
Hyperbilirubinemia	45 (9)	10 (2)	0	4 (2)	2 (1)	0
Proteinuria	35 (7)	7 (1)	0	4 (2)	1 (<1)	0
Anemia	33 (7)	12 (2)	2 (<1)	6 (2)	0	0
Hypophosphatemia	25 (5)	19 (4)	0	1 (<1)	1 (<1)	0

Abbreviations: NCI= National Cancer Institute, CTCAE= Common Terminology Criteria for Adverse Events

efficacy and safety of regorafenib were evaluated in 760 heavily pretreated patients

The aim of the CORRECT trial, an international, multicenter, placebo-controlled phase III trial, was to assess the efficacy and safety of regorafenib in patients with mCRC that progressed after administration of approved standard therapies. A total of 760 patients were randomized to receive either regorafenib (N=505) plus BSC or placebo (N=255) plus BSC. Regorafenib was administered orally at a daily dosage of 160 mg for the first three weeks of each 4-week cycle; mean duration of treatment was 2.8 months for the regorafenib group and 1.8 months for the placebo group.

Patients in both groups had a median age of 61 years and ECOG performance status ≤ 1 was an inclusion criterion. Enrolled patients were heavily pretreated with a median number of 3 prior lines of therapy. 25% of patients (regorafenib group) and 28% of patients (placebo group) had 3, 49% of patients in the regorafenib group and 47% of patients in the placebo group received ≥ 4 previous systemic anticancer therapies and all patients had had previous anti-VEGF treatment with bevacizumab. In the placebo group, more patients progressed on previous treatment with bevacizumab, irinotecan and oxaliplatin than in the regorafenib group. There was a lower proportion of patients with a KRAS mutation in the regorafenib group: 54% of patients assigned to regorafenib and 62% assigned to placebo. 4% of regorafenib group patients and 2% of placebo group patients showed BRAF mutations. Histologically, 98% (regorafenib group) and 96% (placebo group) of patients had adenocarcinomas. The primary endpoint of this trial was OS; secondary endpoints were PFS, objective tumor response rate, disease control rate and safety. Duration of response and stable disease, health-related quality-of-life and health utility values were determined as tertiary endpoints. During the study, plasma and tissue samples were collected for biomarker analysis within a substudy.

median age of 61 years and ECOG performance status ≤ 1

49% (regorafenib group) and 47% (placebo group) of patients received ≥ 4 previous systemic anticancer therapies

Median OS was 6.4 months in the regorafenib group compared to 5.0 months in the placebo group (HR=0.77, 95% CI 0.64-0.94, $p=0.0052$). Median PFS was 1.9 months in the regorafenib arm and 1.7 months in the placebo arm (HR=0.49, 95% CI 0.42-0.58, $p<0.0001$). The OS rate after 3 months of regorafenib treatment was 80.3% compared to 72.7% in placebo group patients. After 6 months, the OS rate was 52.5% in the regorafenib group and 43.5% in the placebo group. After 9 months, the rates were 38.2% in the regorafenib arm and 30.8% in the placebo arm. After 12 months of treatment, the OS rate in both groups was much the same (24.3% in the regorafenib group, 24.0% in the placebo group).

median OS was extended by 1.4 months in the regorafenib group

Subgroup analysis according to site of disease showed better results for regorafenib on OS in patients with colon cancer (HR=0.70, 95%CI 0.56-0.89) than in those with rectal cancer (HR=0.95, 95% CI 0.63-1.44). However, regorafenib had almost the same effect on PFS in patients with colon cancer (HR=0.55, 95% CI 0.45-0.67) as in patients with rectal cancer (HR=0.45, 95% CI 0.33-0.62).

Objective response rates were 1.0% for the regorafenib group and 0.4% for the placebo group, no patients achieved complete response. 41% of patients of the regorafenib arm and 15% of placebo arm patients achieved disease control. The median duration of stable disease was 2.0 months in patients assigned to regorafenib and 1.7 months in patients assigned to placebo.

ORR was 1.0% in the regorafenib group

Overall, treatment-related adverse events occurred in 93% (regorafenib group) and 61% (placebo group) of patients, mostly during treatment cycles 1-2. Grade 3 or 4 treatment-related adverse events were reported in 54% (regorafenib group) and 14% (placebo group). Within the regorafenib group, the most frequent adverse events of any grade were fatigue and hand-foot skin reaction, the most frequent adverse events of grade 3 or higher were hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation. Within the placebo group, the most frequent adverse events of any grade were fatigue and anorexia. Serious adverse events occurred in 44% of patients in the regorafenib arm and in 40% of patients in the placebo arm.

higher rate of treatment-related adverse events of 93% in regorafenib group vs. 61% in placebo group

During the study, a total of 110 deaths were reported (14% in the regorafenib group, 16% in the placebo group), most of them caused by progression

of underlying disease (12% in regorafenib group, 14% in placebo group). 8 (2%) cases of death in the regorafenib group were attributed to adverse events: pneumonia, gastrointestinal bleeding, intestinal obstruction, pulmonary hemorrhage, seizure and sudden death. In the placebo group, 3 (1%) patients died of pneumonia and sudden death. Liver function tests showed a higher incidence of increased liver transaminases and bilirubin in the regorafenib group; one case compatible with drug-induced liver injury due to regorafenib was reported.

Adverse events were the most common cause leading to dose modification (= dose reduction or dose interruption) in 76% (regorafenib group) and 38% (placebo group) of patients. Most frequently, dermatological, gastrointestinal, constitutional, metabolic or laboratory events were causes for dose modification.

health-related quality-of-life and health utility values

Health-related quality-of-life and health utility values were evaluated by:

- ✚ European Organisation for Research and Treatment of Cancer (EORTC) general health status and quality-of-life questionnaire QLQ-C30 (possible score: 0-100, higher scores represent better health-related quality of life). At baseline, mean EORTC QLQ-C30 scores were 62.6 in the regorafenib group and 64.7 in the placebo group. At the end of the treatment, mean scores were 48.9 in the regorafenib group and 51.9 in the placebo group.
- ✚ EQ-5D (EuroQol five dimension) index questionnaire, where higher scores represent better health status. Analysis at baseline showed mean EQ-5D index scores of 0.73 (regorafenib group) and 0.74 (placebo group) versus 0.59 in both groups at the end of the treatment.
- ✚ EQ-5D visual analogue scale evaluation showed scores of 65.4 (regorafenib group) and 65.8 (placebo group) at baseline and 55.5 (regorafenib group) versus 57.3 (placebo group) at the end of the treatment.

6.2 Safety – further studies

meta-analysis evaluated overall incidence of HFSR

This meta-analysis evaluated the overall incidence and the risk of developing hand-foot skin reaction (HFSR) in patients treated with regorafenib [17]. A systematic literature search was conducted and three phase II and two phase III trials (both placebo-controlled) were included in the analysis; data of 1,078 patients having received regorafenib for the treatment of hepatocellular carcinoma, GIST, renal-cell carcinoma and CRC were analyzed. 750 of 1,078 patients received regorafenib as a single agent. In four of five included trials, patients had been pretreated with one or more drugs that could induce HFSR, of which were listed imatinib, sunitinib, bevacizumab, sorafenib and fluoropyrimidines.

highest incidence in patients with renal cell carcinoma, lowest incidence in patients with mCRC

The overall incidence of all-grade HFSR was 60.5% (95% CI: 48.3-71.6), the overall incidence of high-grade HFSR was 20.4% (95% CI: 15.4-26.6). Concerning tumor type, the incidence of HFSR varied significantly; the highest incidence was found in patients with renal-cell carcinoma, the lowest in patients with mCRC.

For relative risk (RR) analysis, only phase III randomized, placebo-controlled trials were included; calculation showed an overall RR of 5.4 (95% CI: 3.76-7.76, $p < 0.001$) for all-grade and an RR of 41.99 (95% CI: 5.88-299.93, $p < 0.001$) for high-grade HFSR for regorafenib compared to placebo.

Comparing the incidences of HFSR in patients treated with regorafenib and patients treated with other multi-kinase inhibitors (pazopanib, sunitinib, axitinib and sorafenib), incidences of both all-grade and high-grade HFSRs were significantly higher for patients treated with regorafenib.

higher incidence in patients treated with regorafenib compared to patients treated with other multi-kinase inhibitors

7 Estimated costs

Regorafenib (Stivarga®) is administered orally at a dosage of 160 mg per day, for the first 21 days of each 28-day cycle. It is available in the form of 40 mg film-coated tablets [3].

For Austria, no cost estimates are available yet. According to manufacturer's information, the list price for a 28-day supply in the United States is \$ 9,350 [18]. Converted into euros, the monthly treatment costs for regorafenib are approximately € 7,035. In Switzerland, the costs for 84 tablets (sufficient for one month of regorafenib treatment) are CHF 5,567 [19], which equals approximately € 4,515.

no cost information for Austria available

In the CORRECT trial, mean duration of treatment was 2.8 months for the regorafenib group [16]. Thus, three months of regorafenib treatment would amount to € 21,105 (U.S. price) and € 13,545 (Swiss price), respectively. Additionally, costs for BSC and management of adverse events incur.

8 Ongoing research

In July 2013 a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted; the following phase III trials were identified:

various phase III studies are ongoing

- 🌐 *NCT01853319*: an open-label phase III study of regorafenib in patients with mCRC who have progressed after standard therapy. The aim of this study is to provide additional information about the safety of regorafenib. The estimated study completion date is July 2014.
- 🌐 *NCT01786538*: a randomized phase III study of oxaliplatin, fluorouracil and leucovorin (FOLFOX) with or without regorafenib in patients with mCRC having progressed after first-line irinotecan plus fluoropyrimidines. The estimated study completion date is May 2017.
- 🌐 *NCT01584830*: a randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in Asians with mCRC who have progressed after standard therapy. The estimated study completion date is May 2014.

- 🚩 **NCT01538680** (EudraCT Number: 2011-005836-25): an open-label phase IIIb study of regorafenib in patients with mCRC who have progressed after standard therapy. The primary endpoint of this expanded-access study will be safety. There are four study locations in Austria. The study completion date has not been specified yet.

Several phase I and phase II studies assessing the use of regorafenib for the first-line or second-line treatment (single-use or combination therapy) of mCRC were identified. For example, one of those studies (NCT01875380, EudraCT Number: 2013-000236-94) aims to evaluate the efficacy and safety of regorafenib in the first-line treatment of patients with mCRC who are frail and/or unfit for polychemotherapy.

Moreover, a database search showed a number of studies investigating the effects of regorafenib on other types of cancer such as gastrointestinal stromal tumors (GIST) or hepatocellular carcinoma.

9 Commentary

regorafenib has been approved by the FDA and the EMA

Regorafenib (Stivarga®) was approved by the FDA in September 2012 [5] for patients with mCRC who have been previously treated with a fluoropyrimidine-, oxaliplatin- and irinotecan based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy (if KRAS wild-type) [3]. In August 2013, the EMA granted marketing authorization for Regorafenib (Stivarga®) for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy)[4].

increase of median OS of 1.4 months in regorafenib group, PFS was improved by 0.2 months in regorafenib group

The CORRECT trial [16], an international, multicenter, randomized, placebo-controlled phase III study evaluated the efficacy and safety of regorafenib in patients with mCRC that progressed after administration of approved standard therapies. Analyses showed a gain of 1.4 months in median OS in the regorafenib group compared to the placebo group (HR=0.77, 95% CI 0.64-0.94, $p=0.0052$). Median PFS was also improved by 0.2 months in the regorafenib group (1.9 months) compared to the placebo group (1.7 months), which results in a hazard ratio of 0.49 (95% CI 0.42-0.58, $p<0.0001$). The objective response rate was 1.0% in patients in the regorafenib group versus 0.4% in patients in the placebo group, suggesting that delay of tumor progression is the primary effect of the described therapy. 41% of patients receiving regorafenib and 15% of patients receiving placebo achieved disease control; the median duration of stable disease was 2.0 months in the regorafenib group and 1.7 months in the placebo group.

primary effect: delay of tumor progression

high incidence of adverse events, occurrence of serious adverse events

The (small) improvements in prolonging OS and PFS survival, and the positive effects on the disease control rate are in contrast to the high incidence of treatment-related adverse events of any grade (93% in the regorafenib group versus 61% in the placebo group). This led to dose modifications in 76% (regorafenib group) and 38% (placebo group) of patients. Adverse events of grade ≥ 3 occurred in 54% of patients in the regorafenib group and 14% of patients in the placebo group. 8 cases of death in the regorafenib arm and 3 cases of death in the placebo arm were attributed to adverse events.

In all clinical trials (a total of 1,100 patients received Stivarga®) 0.3% of patients had severe drug-induced liver injury with fatal outcome. Thus, Stivarga® prescribing information includes a boxed warning for hepatotoxicity [3]. Compared to other anti-neoplastic protein kinase inhibitors like pazopanib, sorafenib and sunitinib, the safety profile of regorafenib is similar (including labeled warnings for teratogenicity, hypertension, hemorrhagic events and QTc prolongation) [20].

The phase III study also aimed to evaluate patients' health-related quality of life and health utility values by using questionnaires (EORTC QLQ-C30 and EQ-5D) and VAS scales. Interestingly, the results in both treatment groups – both at baseline and at the end of treatment – were similar, showing that regorafenib treatment is apparently not responsible for a decrease in health status and quality of life, but does not improve quality of life either.

In the CORRECT trial, regorafenib was administered to patients who ran out of therapeutic options but still had good performance status [21]; 49% of patients (regorafenib group) and 47% (placebo group) of patients had undergone ≥ 4 previous systemic anticancer therapies. The median age of study patients in both groups was 61 years, and all patients had ECOG performance status 0 or 1. Considering the fact that the median age at diagnosis for colon and rectum cancer is about 69 years [11] and previous treatment lines also require time, it is questionable how many patients are effectively eligible for this new drug in third or fourth-line therapy. Especially since verification is still needed of regorafenib as being an appropriate therapeutic option for patients with a poorer performance status than ≤ 1 .

For future research, some questions on regorafenib need to be answered regarding the mechanism of action, its activity in other lines of mCRC therapy and the optimal management of adverse events. Furthermore, identification of biomarkers could help to predict the activity of regorafenib [22]. Based on molecular markers, subgroups of patients who may achieve significantly better survival times on regorafenib need to be identified [23].

In summary, regorafenib may represent a therapeutic option for patients who received all approved standard therapies while maintaining a good performance status. However, the modest gain in OS and PFS survival, the high-risk for adverse events, lack of improvements in QoL and potentially considerable costs of this therapy call into question whether this drug represents a viable treatment option in unselected patients.

**no improvement of
quality-of-life in both
groups**

**applicability of results
needs to be verified**

**detailed criteria for
selecting eligible
patients need to
determined**

**modest survival benefit
stands in contrast to
high incidence of
adverse events and high
costs**

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